

Minoxidil in androgenic alopecia: New formulations with Improved delivery

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ABSTRACT

Background: Minoxidil was introduced into the market as a hypotensive agent, however, after marketing, the hypertrichosis side effect was reported by almost all users. This adverse effect encourages the repositioning or repurposing the use of minoxidil as a topical preparation for the treatment of hair loss.

Objective: topical minoxidil is contemplated as an effective treatment to reduce hair loss and promote regrowth in conditions like androgenetic alopecia. However, the unerring mode of action of minoxidil remains obscure. In this review, the molecular pharmacology of minoxidil, the response of hair follicles to treatment, and the side effects of the topically applied minoxidil were reviewed. The innovation in the formulation of topical preparation toward enhancing delivery was highlighted focusing on the use of nanoemulsion and nanocarrier systems such as nanoparticles and liposomes that enriched the topical delivery.

Keywords: minoxidil, hair loss, topical preparation, nano-carriers.

المخلص:

الخلفية العلمية: تم تسويق دواء المينوكسيديل في السوق كعامل خافض للضغط، ولكن بعد التسويق، تم الإبلاغ عن الآثار الجانبية لفرط الشعر من قبل جميع المستخدمين تقريبًا. شجع هذا التأثير الضار على إعادة استخدام المينوكسيديل كمستحضر موضعي لعلاج تساقط الشعر. في الواقع، يُنظر إلى المينوكسيديل الموضعي كعلاج فعال لتقليل تساقط الشعر وتعزيز إعادة النمو في حالات مثل الصلع الوراثي. ومع ذلك، فإن طريقة عمل المينوكسيديل لا تزال غامضة.

الهدف: في بحث المراجعة هذا تم استعراض علم الأدوية الجزئي للمينوكسيديل واستجابة بصيالات الشعر للعلاج والآثار الجانبية للمينوكسيديل الموضعي. بالإضافة إلى ذلك، تم تسليط الضوء على الابتكارات الحديثة في صياغة المستحضرات الموضعية لغرض تحسين إيصال الدواء مع التركيز على استخدام مستحلب النانو وأنظمة الناقل النانوي مثل الجسيمات النانوية والجسيمات الشحمية التي تثرى التوصيل الموضعي.

الكلمات المفتاحية: مينوكسيديل، تساقط الشعر، مستحضر موضعي، ناقلات النانو.

INTRODUCTION

Hair is an essential part of the human body since it influences self-esteem and optimism across both genders. Everybody wants to have beautiful, strong, and thick hair on their heads as hair has a

significant influence on their appearance and social life (1). Hair is considered as protective appendages along with sweat glands, sebaceous glands, and nail is known as epidermal derivatives which derived from skin ectoderm (2).

Hair structure

Hair is composed of proteins (like keratin), lipids, water, pigments, and other trace matter. Structurally, hair is divided into the bulb, the root and the stem which is embedded in the dermis, particularly in the pilosebaceous follicle. The bulb is the innermost region that is bestowed for hair growth. It is linked to dermal papillae, a highly vascularized region that allow transportation of nutrients to the hair. The root is securely linked to the hair follicle, which is situated in between the bulb and the

epidermal surface, whereby hair develops the shape of the stem (3). Collectively, the root and stem, are known as the hair shaft and are composed of three concentric layers: medulla, cortex, and cuticle. The cortex is the thickest part of hair fiber and it is responsible for the mechanical assets while the cuticle is the next stratum, which is the outer layer of hair that acts as a barrier and protects the hair fiber from the external environment (4). The schematic structure of hair is represented in **figure (1)** (4).

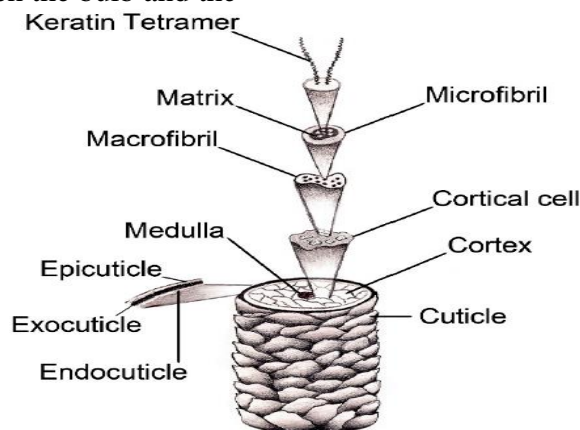


Figure (1) The structure of hair (4)

Hair follicle cycle

Hair follicles are distributed throughout the body surface, with the exclusion of palm, and soles. The continuous cycle of hair follicles includes 3 stages of growth (anagen), involution (catagen) and rest (telogen) as shown in **figure (2)**. The first phase is the generation stage, during which the hair shaft is generated. About 85% of hair follicles on the scalp are in this phase, usually, this phase lasts about 2-3 years. In the second phase, the hair follicle involutes, about only 1% of hair follicles on the scalp

are in anagen phase which is the least amount of hair follicles, normally this phase lasts 2-3 weeks. The last phase is telogen and is known as the latent stage, around 14% of hair follicles on the scalp are in the telogen phase. It lasts 2-3 months (5). In the normal hair cycle, the anagen to telogen ratio is 12:1 (6). The hair shaft generated by terminal follicles is taller than 0.06 mm in diameter and has a bulb situated in the deep dermis, whereas the hair shaft created by vellus follicles is less than 0.03 mm in diameter and has a bulb positioned topically in between papillary and reticular dermis (5).

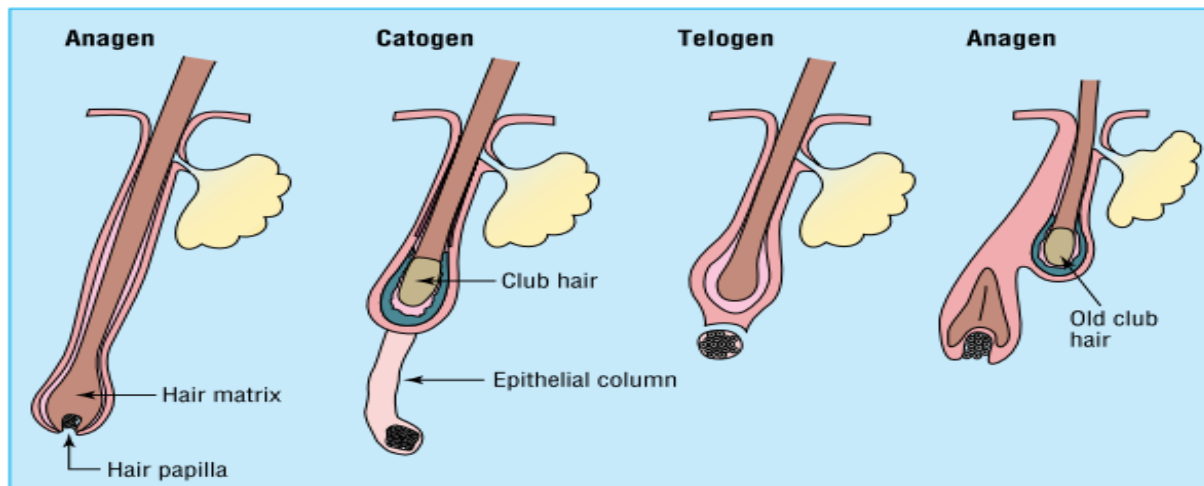


Figure (2) Normal hair cycle (5)

Hair loss or alopecia

Alopecia is one of the utmost prevailing meditative skin ailments of many communities which causes many economical and psychological problems. There are many types of alopecia, the most common one is known as androgenic alopecia (AGA) or Male pattern hair loss (MPHL) (7). AGA is a lenient, emulated hair loss from the scalp, that take place in genetically susceptible individuals.

Androgenetic alopecia is widespread and its incidence rises with age, impinging more than one-half of males older than 50 years and nearly 73 % of men and 57 % of women over 80 years old (8). The hair loss in AGA results from programmed and lenient miniaturization of the hair follicle and alteration in hair cycle enterprising (9). The anagen phase of hair shortens and the telogen phase lengthens with each cycle and the anagen to telogen proportion decreases from 12:1 to 5:1. When the anagen phase shortens in repeated cycles, the fresh anagen hair develops weaker and finally fails to deliver the outer layer of skin. Instead, the telogen phase elongates, the telogen hair is

more loosely attached to the follicle than do anagen hair, and hair shedding is observed during washing the hair. Furthermore, the number of hairs found on the scalp will be mitigated as the quiescent time between telogen hair falling and anagen regeneration lengthens (10). As androgenic alopecia is an androgen-dependent condition, it can start soon after puberty. Many studies suggested that baldness occurs as a result of increased concentration of dihydrotestosterone (DHT) and androgenic receptors (11). The pathogenic mechanism of AGA is uncertain; nevertheless, it is known that AGA promotes hair follicle shrinkage, reduces hair density, and increases the appearance of weak vellus hair. The shortening of the anagen phase leads to a drop in the hair density and a decrease in the diameter of the hair follicle (reduced thickness) (12).

Therapeutic Approach

Androgenic alopecia is progressive, and requires treatment for a long time and lifelong compliance for continued improvement. The main goal of treatment is to enhance hair density and reduce miniaturization. There is a wide range of modalities used in the treatment of

androgenic alopecia and include pharmacological therapy, physical therapy, and emerging therapy.

Pharmacological therapy

- Oral and Topical Minoxidil
- Oral 5 Alpha reductase inhibitors (Finasteride, Dutasteride)
- Oral and Topical Prostaglandins (Latanoprost, Bimatoprost)
- Topical valproic acid
- Oral Serenoa Repens/Saw Palmetto

Physical therapies

- Growth factors (Platelet-rich plasma (PRP))
- Micro-needling
- Laser therapy (Low-level laser therapy (LLLT), Fractional laser)

Emerging therapies

- Immunosuppressants (Ciclosporine)
- Phosphodiesterase 5 (PDE5) inhibitors (Sildenafil)

c. Minerals and vitamins

Patients with hair loss can have a variable response to the above treatments. So far, FDA approved drugs for male-pattern baldness are finasteride (oral) and minoxidil (topical) (13).

Minoxidil

Minoxidil (chemical formula; $C_9H_{15}N_5O$, 6-piperidin-1-ylpyrimidine-2,4-diamine 3-oxide), and the chemical structure is shown in **figure (3)**. Minoxidil was incipiently popularized as an oral hypotensive medication. One of the reported adverse effects of minoxidil is hypertrichosis affecting 24-100% of patients using minoxidil and this was behind using minoxidil topically in the treatment of androgenic alopecia. The US FDA authorized a dermal formulation of minoxidil 2% and 5% in male-patterned baldness in 1988 and 1991, respectively. In 1991, a dermal formulation of minoxidil 2% was authorized for female patterned alopecia (14).

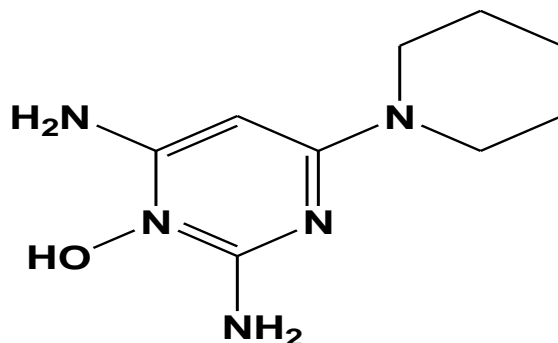


Figure (3) Chemical structure of minoxidil

In addition, minoxidil has just been advised as an off-label drug to control other kinds of hair loss such as alopecia areata (AA), scarring alopecia, and hair shaft issues, as well as to encourage body hair production in other areas such as the brows and beard (15).

Minoxidil mechanism of action

Minoxidil itself is a prodrug and requires activation by hepatic sulfotransferase enzyme which metabolizing the drug to the active metabolite, minoxidil N-O sulfate. Minoxidil is an effective vasodilator that acts by opening the ATP- dependent potassium channel located in the smooth muscles of the peripheral arteries, allowing

potassium efflux that causes hyperpolarization and relaxation of smooth muscle. Minoxidil is similar to hydralazine and diazoxide in producing arteriolar vasodilation with actually no action on the capacitance vessels. Minoxidil increases blood flow to organs like skin, GIT, skeletal muscles, and the heart more than to CNS (16). The antihypertensive effect and follicular effect of minoxidil are linked to its conversion to minoxidil sulfate, the active metabolite (17).

The existence and function of the sulfotransferase enzyme in the hair follicle differ from one individual to another, and the reactivity to the medication is connected to converting minoxidil to its activated state (18). Patients using medications that increase the level of sulfotransferase enzyme-like tretinoin potentiate the effect of topical minoxidil but its use is limited due to irritation while those drugs that reduce sulfotransferase enzyme level, such as aspirin, attenuate the minoxidil action (19,20).

Hair follicle response to minoxidil

The unerring mode of minoxidil stimulation of hair growth is obscure, but there are many ways through which the drug can treat AGA. It may change the hair cycle which either prolonging anagen or shortens telogen, enhances linear hair growth rate, increase the diameter of the hair fiber, enlarge miniaturized follicles, or combination of more than one mechanism (21). Basically, minoxidil mode of action is based on blocking of calcium entry to the cells following potassium channel opening; this step will mediate nitric oxide production with associated vasodilation which will result in replenishing of the hair follicle with blood and nutritional substances resulting in growth or regeneration. Since numerous adenosine receptors are expressed in dermal papilla cells (DPCs), research discovered

adenosine to be a messenger for minoxidil-promoted vascular endothelial growth factor (VEGF) production in DPCs, which induces angiogenesis and eventual hair growth stimulation (12).

Minoxidil affects the hair follicles of androgen and non-androgen-dependent areas. Since the drug is considered as a potent vasodilator and the drug's effect is independent on neither inhibition of 5 alpha-reductase nor hormonal factor (15).

Animal and human studies on minoxidil action on hair growth

Mori and Uno conducted profound research on the impact of dermal minoxidil usage on the hair cycle in rats, and their findings revealed that the telogen phase was shortened from 20 days in normal non-treated rats to 1-2 days in minoxidil-treated animals, with no impact on the timeframe of the anagen phase. The influence of minoxidil on hair growth in the stump-tailed macaque, a monkey that suffers post-adolescent baldness in the scalp is similar to their effect on human androgenic alopecia. This finding indicated that minoxidil can minimize hair loss and increase hair growth in these animals (22). Since investigation on the usefulness of external minoxidil on androgenic alopecia has been limited, the information about the influence of minoxidil on decent hair growth was little. In male or female conditioned baldness, the use of dermal minoxidil in concentrations of 2%-5% showed a steady therapeutic outcome and raise in hair growth within 2 months of treatments, with maximum effect reversal within 6 months. Headington and Novak investigated the impact of minoxidil therapy on hair diameter and reported that minoxidil might enhance hair diameter in males with baldness after 3 months of treatment (21).

Minoxidil sulphation

The active component relevant for antihypertensive action owing to the fast

relaxing of vascular smooth muscles is minoxidil sulphate (23). Sulphotransferase enzymes catalyze the transformation of minoxidil to its active metabolite, and the activity of such enzymes has been identified in the human hepatic tissue (24), rat liver (25), human platelet (26), human keratinocyte (27), mouse vibrissae follicles (28), rat pelage, and rat keratinocytes (18,29). So far, five human sulphotransferase genes have been identified, each expressing for one of three types of enzymes necessary for sulphating phenols and catecholamines, estrogens, and hydroxysteroids (30,31). In human scalp skin, the minoxidil sulphation catalyzed by two phenol sulphotransferase and in human epidermal keratinocyte biochemical evidence supported the presence of mRNA expression for four sulphotransferases enzyme (31,32). The enzyme activity in the scalp is subjected to high inter-individual variations and it is connected to the level in platelets. From a clinical point of view, those men who responded well to minoxidil showed higher activity of scalp sulphotransferase activity compared with those who did not respond (32).

Minoxidil therapeutic use in androgenic alopecia

Oral minoxidil is no longer used because of its potential side effects, however topical minoxidil has comparable advantages (6). According to meta-analysis research, cutaneous minoxidil therapy at all doses exhibited a greater response than the placebo group, with average differences of 8.11 hairs/cm² linked with 2% minoxidil and 14.90 hairs/cm² associated with 5% minoxidil therapy compared to the control group. A 5-year follow-up study on 31 individuals with baldness treated with 2% and 5% minoxidil found that maximal hair restoration appeared after one year (33). Numerous clinical studies using cutaneous minoxidil have been undertaken, and

multiple doses in various formulations have been attempted to examine their effectiveness. In males with androgenic alopecia, minoxidil solution 5% performed better than the 2% and placebo groups, with a massive rise in the mean difference in hair density in both male and female subjects (34,35). Nonetheless, 2% minoxidil formulation were preferred over 5% due to the association of the latter with unpleasant effects (headaches and dermatitis) (36). In Asian women, 1% minoxidil solution estimated to be effective with significant enhancement of non-vellus hair compared to the placebo group (37).

Minoxidil adverse effect

Topical minoxidil is premeditated as vindicating with curbed local scalp adverse effects. Induced hair loss (telogen effluvium) which is considered a prevailing side effect of minoxidil and the process commonly known as shedding, this usually occur due to the minoxidil causes induction of hairs in the telogen phase to shed as early as possible before beginning anagen phase. The treatment with topical minoxidil solution required long-term application for getting benefits and over time some patients may develop contact dermatitis to minoxidil itself or a specific ingredient in the preparation. The most common complaint among minoxidil solution users is scalp pruritus, itching, and scaling (38). The incidence of these adverse effects is higher with 5% minoxidil solution than it was in 2% solution. Although an allergic reaction to minoxidil could happen, it is scarce. Preliminary studies revealed that 5.7 percent of patients using the 5% formulation and 1.9 percent of individuals utilizing the 2% formulation experienced an application site response. Because the 5% formulation includes more propylene glycol (50%) than the 2% preparation, which only contains 30%, the greater strength is associated with a significantly increased occurrence of

itching, dryness, and erythema. For people who are allergic to propylene glycol, another vehicle such as butylene glycol, glycerin, or polysorbate should be used instead (39,40).

External application of minoxidil can also induce hair growth in areas other than the scalp. This effect depends on the concentration which is more pronounced by 5% solution than 2%. The common areas affected are cheeks, temples, forehead and it was occurred due to contamination of these areas. The systemic effect is not certain, so hypertrichosis is less likely in areas far from the face. Hypertrichosis occurs more commonly in women than in men and it affects 9% of females and 1% of males that applied topical minoxidil solution 5%. Fortunately, this side effect is reversible and resolves within 4-5 months after termination of treatment (41). The usual daily dose of topical minoxidil is twice a day. However, the excessive application of high doses associated with increased systemic uptake with the resultant more systemic side effect (42).

Minoxidil topical preparations

Because of the drug's poor aqueous solubility, conventional marketed topical preparations of minoxidil, such as spray, solution, foam, and shampoo, in concentrations ranging from 1 to 5%, are currently formulated with organic solvents and co-solvents like ethanol and propylene glycol. Long-term use of current organic solutions causes the formation of minoxidil crystals due to ethanol evaporation, which may result in many undesired side effects like scalp pruritus, itching, and scaling as mentioned earlier which limit its usefulness (38,39). Another major drawback to such preparations is the short contact time to the scalp. Because local vasodilation causes hair growth, the quicker the contact period of the medication solution with the scalp, the more treatments are necessary for therapeutic

efficacy. As a result, there is a need to maximize the contact time during which the local drug concentration increases, resulting in improved vasodilation. In recent years, an attempt has been made to increase the contact time, enhance skin drug transdermal penetration to the scalp hair follicles and attain the controlled release of drug for a prolonged period which may help patients in reducing the frequency of application and achieve better compliance (43). Thus, there is a need to develop an innovative transdermal drug delivery system that can overcome the limitations of conventional formulations using approaches to increase diffusivity and transfollicular targeting by incorporation of minoxidil in nanocarrier for topical treatment of androgenic alopecia (44).

There are many types of nanocarriers which include: solid lipid nanoparticles (SLNs), niosomes, liposomes, microemulsions, nanostructured lipid carriers (NLCs), etc.(45).

Minoxidil formulation using nanotechnology

SA Cardoso *et al.* planned to acquire a dermal nanoemulsion loaded with minoxidil in a trial to improve follicular permeation and controlled drug delivery in the treatment of alopecia areata. Compared to the control alcoholic solution, the tailored nanoemulsions displayed nearly Two-folds the action of sustained release. When compared to standard ethanol-based solutions, nanoemulsions enhanced the minoxidil skin penetration by more than 9 times. According to follicular deposition and diffusion experiments, minoxidil nanoemulsions penetrated hair follicles 26 times more efficiently than a standard treatment (44).

Kumar Pawan *et al* investigated the continuous release of minoxidil into follicles

using self-assembled nanovesicles of oleic acid and phosphatidylcholine. An *in-vitro* drug release research revealed the regulated discharge of minoxidil from the vesicular gel. In terms of minoxidil accumulation in the stratum corneum (SC) and remnant skin, the generated minoxidil vesicular gel (0.2 percent) outperformed minoxidil lotion (2 percent) with enhancement ratios of 3.0 and 4.0, respectively. When compared to the control, vesicular gel showed enhanced minoxidil deposition into hair follicles by a factor of ten (46).

Eman Abd et al. created a minoxidil nanoemulsion for improved skin delivery using oleic acid and eucalyptol oil as the oil phase and permeability stimulant, respectively. When conducting an *in-vitro* permeability investigation, they discovered that minoxidil infiltration from nanoemulsions was better than the diffusion from the control solution. When compared to the control, the nanoemulsion system produced considerably larger fluxes, which might be due to improvements in both minoxidil stratum corneum solubility and skin diffusion in nanoemulsion systems (47).

Wang Wenxi, *et al.* developed minoxidil-loaded nanostructured lipid carriers (NLCs) using oleic acid as a liquid lipid and stearic acid as a solid lipid for improving skin penetration after topical administration for the management of androgenic alopecia. When the minoxidil-loaded NLCs formulation was compared to the solid lipid nanoparticles (SLNs), it was found that the NLCs released minoxidil faster than the minoxidil-loaded SLNs. Minoxidil-loaded NLCs showed a more prominent permeation

and retention profile than minoxidil-loaded SLNs in an *in vitro* skin permeation study. Following the delivery of minoxidil NLCs, no erythema was seen (48).

Minoxidil-encapsulated poly (L-lactide-co-glycolide) nanoparticles (PLGA nanoparticles) were designed for the appropriate treatment of androgenetic alopecia. Using W/O/W solvent evaporation and sonication, nanoparticles were evaluated for their ability to entangled minoxidil in hair follicles. Minoxidil-encapsulated PLGA nanoparticles provided 3.1 times more minoxidil in the stratum corneum and 2.5 times more minoxidil in hair follicles eight hours after treatment compared to minoxidil aqueous solution. Furthermore, the study observed that hair follicles got about 5 percent of the minoxidil-encapsulated PLGA nanoparticles dose (49).

Conclusion:

Minoxidil is a commonly used agent for the treatment of hair loss and it is a relatively safe product. However, the treatment with topical minoxidil solution required long-term application with relative application of high doses, which may develop contact dermatitis to minoxidil itself or a specific ingredient in the preparation. Moreover, this may be associated with increased systemic uptake with resultant in more liability for systemic side effects. Thus, the use of nanocarrier and other advance nanoparticulate system in the formulation of minoxidil is considered to improve permeation into the hair follicles with remarkable benefits to patients with hair loss.

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